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54 Title: USE OF CARBOHYDRATES FOR PROMOTING SKIN EXFOLIATION

57 Abstract

The use of carbohydrate derivatives in or for making a topical composition for promoting skin exfoliation is disclosed. The use of said composition for controlling intrinsic and extrinsic skin ageing, as well as a non-therapeutic skin treatment method for skin exfoliation, are also disclosed.

# USE OF CARBOHYDRATES FOR PROMOTING SKIN EXFOLIATION

The invention relates to the use of carbohydrate derivatives in or for producing a cosmetic and/or dermatological composition to promote skin exfoliation and/or to control the intrinsic and extrinsic aging of the skin. It also relates to a non-therapeutic treatment method intended to exfoliate the skin as well as a non-therapeutic method for the treatment of skin aging.

Skin aging resulting from effects on the skin of intrinsic or extrinsic factors is reflected by the appearance of wrinkles and lines, by the yellowing of the skin which develops a parchment appearance accompanied by the appearance of pigmented spots, by the disorganization of the fibers of elastin and collagen bringing about a loss of elasticity, suppleness and firmness and by the appearance of telangiectasias.

Some of these signs of aging are more particularly linked to intrinsic or physiological aging, that is, "normal" aging associated with age, while others are more specific to extrinsic aging, that is, the aging in general caused by the environment; this involves more particularly photo-aging due to exposure to the sun, light or any other radiation.

The invention is concerned with intrinsic or physiological aging as well as with extrinsic aging.

The changes in the skin due to intrinsic aging are the result of genetically programmed senescence in which endogenous factors are involved. This intrinsic aging in particular causes a slowing-down of the renewal of skin cells, which is reflected mainly in the appearance of clinical changes such as the reduction of subcutaneous adipose tissue and the appearance of fine lines or wrinkles, and by histopathological changes such as an increase in the number and thickness of elastic fibers, a loss of vertical fibers of the elastic tissue membrane, and the presence of large irregular fibroblasts in the cells of this elastic tissue.

In contrast, extrinsic aging brings about clinical changes such as deep wrinkles and the formation of a lifeless, tanned skin, and histopathological changes such as an excessive accumulation of elastic material in the upper dermis and a degeneration of the collagen fibers.

Various agents intended to control skin aging are known in the prior art.

Thus, US patent 4,603,146 describes the use of retinoic acid and its derivatives in cosmetic compositions to control skin aging.

Moreover, numerous patents and publications (see for example the application EP-A-413 528) as well as many commercial cosmetic compositions teach the use of α-hydroxy acids such as lactic acid, glycolic acid or citric acid to treat skin aging.

Finally, the beta-hydroxy acids and more particularly salicylic acid and its derivatives are known for their exfoliating properties (see the documents WO-A-93/10756 and US-A-4,767,750).

All these compounds have an action against skin aging consisting of exfoliation, that is, the elimination of "dead" cells situated at the surface of the *stratum corneum*. This exfoliating property is also called, often incorrectly, the keratolytic property. However, some compounds also have secondary effects, which consist in tingling, pulling, overheating and redness that are unpleasant for the user.

It is observed, therefore, that there is a need for anti-aging agents having an action that is at least as effective as that of compounds of the prior art, but without their disadvantages.

Furthermore, Brysk (Cell and tissue research 253, 657-663, 1988; Expl. Cell Biol. 57, 60-66, 1989) showed the part played by the glycoproteins in the cohesion of the *stratum corneum*. She also demonstrated the inhibitory action of certain carbohydrates, in particular amino carbohydrates, with respect to the cohesion of the *stratum corneum*.

The applicant has unexpectedly discovered that certain carbohydrate derivatives display a very substantial activity inhibiting the cohesion of the stratum corneum, greater than the action of analogous derivatives already known for this activity.

Consequently, the topical application of these new derivatives permits the exfoliation of the skin and control of skin aging.

Of course, the use in a topical application, for the treatment of dry skin, of amides from the condensation of an acid carbohydrate and a primary amine is known from the document US-A-5,084,270. However, an exfoliating action on the skin is neither mentioned nor suggested for these products in the prior art.

The document WO95/05155 describes lipophilic derivatives of sugars, and their use in a cosmetic vehicle as modulators of the synthesis and/or excretion of elastase from fibroblasts. However, an exfoliating action of carbohydrate derivatives is neither mentioned nor suggested in this document.

The present invention has as its subject the use in or for the production of a topical composition, in the cosmetic, dermatological and/or pharmaceutical areas to promote the exfoliation of the skin, of at least one carbohydrate or carbohydrate derivative corresponding to the formula (I),

R-X-A (I)

in which A represents a chain composed of one to twenty carbohydrate or carbohydrate derivative units, each including 3 to 6 carbon atoms, mutually linked, preferably by acetal bridges, each of these units possibly being substituted, for example by a halogen, an amine function, acid function, ester function, thiol, alkoxy function, thio-ether function, thio-ester function, amide function, carbamate function, or urea function,

R represents an alkoyl chain or an alkenyl chain containing 4 to 24 carbon atoms, branched or linear, capable of being interrupted by ether bridges, possibly bearing a hydroxyl function, a carboxylic acid function, an amine function, an ester function, an acyloxy function, an amide function, an ether function, a carbamate function, or a urea function,

X represents a function linking R and A, such as for example an amine, ether, amide, ester, urea, carbamate, thioester, thioether, or sulfonamide function.

The invention also has as its subject the use of carbohydrates such as described above to control skin aging.

Preferably, R represents an alkoyl chain or an alkenyl chain, containing 4 to 24 carbon atoms, branched or linear, possibly bearing a hydroxyl function.

Each of the carbohydrate units composing A can be a sugar or sugar derivative. For example, each unit composing A can be a reduced sugar, an amino sugar or a sugar bearing a carboxylic acid function.

Among the sugars or sugar derivatives that can enter into the constitution of A may be cited for example the following products, which are commercially available, possibly in the form of the salt: N-acetyl-D-galactosamine, N-acetyl-D-glucosamine, N-acetylneuraminic acid, adonitol, β-D-allose, D-altrose, 6-amino-6-deoxy-D-glucose, 1,6-anhydroglucose, arabinic acid, arabinogalactan, D-arabinose, L-arabinose, D,L-arabinose, D-arabitol, L-arabitol, D-cellobiose, D-glucosamine, D-galactosamine, 2-deoxy-D-glucose, 6-deoxy-D-galactose, 6-deoxy-L-galactose, galactitol, mesoerythritol, D-erythrose, D-fructose, D-fucose, L-fucose, D-galactaric acid, galactitol [sic], galactomannan, D-galactono-1,4-lactone, L-galactono-1,4-lactone, D-galactosamine, D-galactose, L-galactose, D-galacturonic acid, β-gentobiose, glucamine, D-glucaric acid, D-glucaric acid [sic], D-glucono-1,5-lactone, L-glucono-1,5-lactone, D-glucosamine, D-glucosaminic acid, D-glucuronic acid, L-glucose, D-glucose, isomaltitol, isomaltotriose, isomaltose, lactobionic acid, D-lactose, lactulose, D-lyxose, L-lyxose, lyxosamine, maltitol, D-maltose, maltotetraose, maltotriitol, maltotriose, D-mannosamine, D-mannose, L-mannose, D-melezitose, D-melibiose, D-raffinose, D-raffinose undeca-acetate, L-rhamnose, D-ribose, L-ribose, D-ribulose, rutinose, D-saccharose, α-sophorose, sorbitol, D-tagatose, D-talose, D-threose, turanose, D-xylitol, D-xylose, L-xylose, and D,L-xylose.

Preferably, A will be chosen from among the following hydrocarbon chains:

D-glucosamine or 2-amino-2-deoxy-D-glucose, D-glucamine or 1-amino-1-deoxy-D-glucitol, -methyl-glucamine, D-glucose, D-maltose, sorbitol, maltitol.

Preferably, R contains 4 to 16 carbon atoms such as for example the n-butyl, n-octyl, 2-ethylhexyl, n-dodecyl radicals.

According to the invention, the preferred compounds will include at least one product chosen from among:

N-butanoyl-D-glucosamine, N-octanoyl-D-glucosamine, N-octyloxycarbonyl-N-methyl-D-glucamine, N-2-ethyl-hexyloxycarbonyl-N-methyl-D-glucamine, 6-O-octanoyl-D-glucose, 6'-O-octanoyl-D-maltose, 6'-O-dodecanoyl-D-maltose.

The preparation of the products (I) is well known by one skilled in the art. Reference may be made for example to the following documents: FR-A-2703993, FR-A-2715933. EP-A-577506, EP-A-566438, EP-A-485251.

In the compositions according to the invention, the carbohydrate according to (I) or the mixture of carbohydrates according to (I) can be used in a quantity of from 0.05 to 20% by weight relative to the total weight of the composition and in particular in a quantity of from 0.2 to 10%, and better from 0.5 to 5% by weight relative to the total weight of the composition.

In the compositions that can be used according to the invention, the carbohydrates corresponding to the formula (I) can be combined with other active substances having exfoliating properties, such as the hydroxy-acids, α- or β-keto-acids, retinoids, and certain sulfonic acids. Such a combination makes it possible to reduce the active concentration of the latter because of additive effects. In this way a less irritating and less toxic composition can be obtained as well as a more efficacious composition than

those of the prior art using only these active substances.

The hydroxyacids can be for example α-hydroxyacids or β-hydroxyacids, which can be linear, branched or cyclic, saturated or unsaturated. The hydrogen atoms of the carbon chain can in addition be substituted by halogens, or halogenated, alkylated, acylated, acyloxylated, alkoxy carbonylated or alkoxylated radicals having 2 to 18 carbon atoms.

These hydroxyacids are in particular glycolic, lactic, malic, tartaric, and citric acids and in general fruit acids, 2-hydroxy-alkanoic, mandelic, and salicylic acids, as well as their alkylated or acylated derivatives such as n-octanoyl-5-salicylic acid, n-dodecanoyl-5-salicylic acid, n-decanoyl-5-salicylic acid, n-octyl-5-salicylic acid, n-heptyloxy-5- or -4-salicylic acid, or 2-hydroxy-3-methylbenzoic acid or their alkoxylated derivatives such as 2-hydroxy-3-methoxybenzoic acid.

The retinoids can be in particular retinoic acid, (all-trans or 13-cis) and its derivatives, retinol (Vitamin A) and its esters such as retinol palmitate, retinol acetate and retinol propionate, as well as their salts, or also retinal.

As an example, hydroxyacids, ketoacids and retinoids can be introduced into the compositions used according to the invention in a quantity representing from 0.01 to 5% by weight of the total weight of the composition, and better from 0.1 to 3%.

In order to control photo-aging effectively, it is also possible to add to the composition used according to the invention one or several additional sun screens, active in the UVA and/or UVB, hydrophilic or lipophilic, possibly including a sulfonic function.

A test to measure the efficacy of the carbohydrates was carried out in vitro.

Brysk (Cell and tissue research 253, 657-663, 1988; Differentiation 32, 230-237, 1986) showed that hemagglutination constituted a reliable model for the study of corneocytic cohesion: she demonstrated hemagglutination due to a glycoprotein of the *stratum corneum*, as well as a simultaneous inhibition by the same amino sugars of the hemagglutination and of the cohesion of the *stratum corneum*.

The test principle is based on the fact that lectin causes the agglutination of erythrocytes.

The products to be tested, prepared at various dilutions, are added to solutions of lectin. The minimum concentration of a product permitting inhibition of the hemagglutination caused by the lectin is measured.

The most efficacious products are those displaying inhibitory activity at the lowest possible concentration.

The results of these tests show an activity of products used according to the invention at concentration well below the minimum active concentrations of the state of the art products tested as references (see below).

The invention also has as its subject a cosmetic or dermatological skin treatment method intended to exfoliate the skin, consisting of applying to the skin a composition containing at least one carbohydrate of formula (I), in a cosmetically and/or dermatologically acceptable medium.

The invention also has as its subject a cosmetic or dermatological method for the treatment of skin aging, consisting of applying to the skin a composition containing at least one carbohydrate as defined above, in a cosmetically and/or dermatologically acceptable medium.

The composition used according to the invention contains a cosmetically or dermatologically acceptable medium, that is, a medium compatible with the skin, nails, mucosa, tissues and hair. The composition containing one or several carbohydrates (I) can be applied by the topical route to the face, neck, hair, mucosa and nails or any other skin area of the body.

The compositions used according to the invention can be in all the forms suitable for topical application, in particular in the form of aqueous, aqueous-alcoholic or oily solutions, dispersions of the lotion or serum type, aqueous, anhydrous or oily gels, emulsions with a liquid or semi-liquid consistency of the milk type, obtained by dispersion of a fatty phase in an aqueous phase (O/W) or the reverse (W/O), suspensions or emulsions with a soft, semi-solid or solid consistency of the cream type, gel, microemulsion type or microcapsules or microparticles or vesicular dispersions of the ionic and/or non-ionic type. These compositions are prepared by the usual methods.

They can also be used for the hair in the form of aqueous, alcoholic or aqueous-alcoholic solutions, or in the form of lotions, gels, emulsions, mousses, or also in the form of compositions for aerosols also containing a propellant under pressure.

The quantities of the various constituents of the compositions used according to the invention are those traditionally used in the areas under consideration.

These compositions constitute in particular creams for the protection, treatment or care of the face, hands or body, milks for body protection or care, lotions, gels or mousses for the care of the skin and mucosa or for the cleansing of the skin.

The compositions can also consist of solid preparations constituting soaps or cleansing bars.

In a well-known manner, the composition used according to the invention can also contain adjuvants common in the cosmetic and dermatological areas such as hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active substances, preservatives, antioxidants, solvents, perfumes, fillers and colorants. The quantities of these different adjuvants are those traditionally used in the areas under consideration, for example from 0.01 to 20% of the total weight of the composition. These adjuvants, depending on their nature, can be introduced into the oily phase, the aqueous phase, and/or into lipid spherules.

As oils that can be used in the invention may be cited the mineral oils (vaseline oil), vegetable oils (shea oil, sweet almond oil), animal oils, synthetic oils, silicone oils (cyclomethicone) and fluorinated oils (perfluoropolyethers). Also useful as fatty materials are the fatty alcohols, fatty acids (stearic acid), or waxes (paraffin, carnauba, beeswax).

As emulsifiers that can be used in the invention may be cited Polysorbate 60 and sorbitan stearate, sold respectively by the trade names Tween 60 and Span 60 by the ICI company. To these may be added the co-emulsifiers such as PPG-3 myristyl ether sold under the trade name Emcol 249-3K by the Witco company.

As solvents that can be used in the invention may be cited the lower alcohols, notably ethanol, isopropanol, and propylene glycol.

As hydrophilic gelling agents can be cited the carboxyvinyl polymers (carbomer), the acrylic copolymers such as the acrylates/alkylacrylates copolymers, polyacrylamides, polysaccharides such as hydroxypropylcellulose, natural gums (xanthan) and clays, and as lipophilic gelling agents may be cited the modified clays such as the bentonites, metallic salts of fatty acids such as aluminum stearates, hydrophobic silica, polyethylenes and ethylcellulose.

As hydrophilic active substances may be used the proteins or protein hydrolyzates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, water-soluble vitamins, starch, bacterial or plant extracts, in particular Aloe Vera.

As lipophilic active substances may be used tocopherol (Vitamin E) and its derivatives, essential fatty acids, ceramides, essential oils.

The carbohydrates according to the invention can be combined with, among other things, active agents intended in particular for the prevention and/or treatment of skin disorders. Among these active agents may be cited for example:

- agents modulating the differentiation and/or proliferation and/or pigmentation of the skin such as Vitamin D and its derivatives, estrogens such as estradiol, kojic acid or hydroquinone;

- anti-free radical agents, such as alpha-tocopherol or its esters, superoxide dismutases, certain metal chelating agents, or ascorbic acid and its esters.

Moreover, the carbohydrates of the invention may be combined with antagonists of substance P and/or CGRP (Calcitonin Gene Related Peptide or peptide linked to the calcitonin gene) such as Iris Pallida and strontium salts, in particular strontium chlorides and nitrates, or antagonists of substance P and/or CGRP such as those described in the French patent applications filed in the name of the applicant under the numbers 9405537 and 9500900. Such a combination makes it possible to guarantee complete tolerance of these compositions, even for very sensitive skins.

The cosmetic or dermatological treatment method of the invention can be effectuated in particular by applying the hygienic, cosmetic or dermatological compositions as defined above, in accordance with the usual technique of use of these compositions. For example: application of creams, gels, serums, pomades, lotions, or milks to the skin, scalp, nails and/or mucosa.

The following examples illustrate the invention. In these examples, the proportions indicated are percentages by weight.

Examples

Example 1: Preparation of 6'-O-octanoyl-β-D-maltose

*A. Activation of octanoic acid*

Into a 500-ml flask provided with a stirring system, thermometer, and reflux condenser with a calcium chloride trap are introduced 12.6 g (0.103 mole) isopropyl chloroformate and 100 ml tetrahydrofuran.

To the mixture, stirred and cooled to -10°C, is added dropwise a solution constituted of 14.4 g (0.1 mole) octanoic acid, 10.4 g (0.103 moles) triethylamine dissolved in 100 ml tetrahydrofuran. During the addition, the temperature is held at between -10°C and -15°C, then at the end, the mixture is allowed to return to ambient temperature and the triethylamine salts are removed by filtration.

*B. Preparation of 6'-O-octanoyl-β-D-maltose*:

Into a 2-liter flask provided with a stirrer and a reflux condenser, is introduced 108 g (0.3 mole) maltose monohydrate dissolved in 540 ml pyridine. To this mixture is added the activated octanoic acid solution prepared in A, and it is left to stir at ambient temperature for 17 hours. The reaction medium is then concentrated under vacuum then taken up in a mixture of solvents (150 ml ethyl acetate, 150 ml heptane, 300 ml water). The medium is permitted to decant, the aqueous phase is isolated then washed twice with 250 ml of an ethyl acetate/heptane mixture (1:2). Finally, the 6'-O-octanoyl-D-maltose is extracted using an ethyl acetate/butanol mixture (2:1). After evaporation of the solvents, 13.1 g 6'-O-octanoyl-β-D-maltose is recovered (yield 28%).
Melting point: 226°C

The $H^1$ and $C^{13}$ NMR spectra are in conformity with the structure of the product.

Elemental analysis:

| | C | H | O |
|---|---|---|---|
| Calculated | 51.3 | 7.7 | 41 |
| Found | 51.2 | 7.8 | 40.9 |

Example 2: Preparation of 6-O-octanoyl-α-D-glucose

Into a 2-liter flask provided with a stirrer and a reflux condenser are introduced 72 g (0.4 mole) anhydrous glucose dissolved in 860 ml pyridine. To this mixture is added the activated octanoic acid solution prepared in Example 1-A, and it is left to stir at ambient temperature for 17 hours. The reaction medium is then concentrated under vacuum then taken up in a mixture of water and acetonitrile and washed three times with an ethyl acetate/heptane mixture (1:1). The aqueous phase is isolated and the 6-O-octanoyl-α-D-glucose is extracted with an ethyl acetate/butanol mixture (2:1). After evaporation of the solvents, the medium is taken up in 60 ml hot acetonitrile. The 6-O-octanoyl-α-D-glucose crystallizes out when the solution is allowed to return to ambient temperature. After filtration and drying, 14.6 g 6-O-octanoyl-α-D-glucose [typo in original] is recovered (yield 48%).

Melting point: 128°C

The $H^1$ and $C^{13}$ NMR spectra are in conformity with the structure of the product.

Elemental analysis:

| | C | H | O |
|---|---|---|---|
| Calculated | 54.9 | 8.5 | 36.6 |
| Found | 55.1 | 8.5 | 36.3 |

Example 3: Preparation of N-octyloxycarbonyl-N-methyl-D-glucamine

In a 1-liter reaction flask, 24.37 g (0.125 mole) N-methyl-D-glucamine is dissolved in 650 ml water and 850 ml tetrahydrofuran with stirring, then 42 g (0.5 mole) sodium bicarbonate is added and the

temperature is brought to 5°C. 24.06 g (0.125 mole) octyl chloroformate is added dropwise, keeping the medium at 5°C for one hour after the addition. The medium is brought to ambient temperature, filtered and decanted. The organic phase is recovered, the solvent evaporated under vacuum and the residue is taken up in 1.5 l acetone under reflux. The N-octyloxycarbonyl-N-methyl-D-glucamine precipitates in the cold. Filtration and drying yields 24 g product (55%).

Melting point: 128°C

The $H^1$ and $C^{13}$ NMR spectra are in conformity with the structure of the product.

Elemental analysis: N-octyloxycarbonyl-N-methyl-D-glucamine.½ $H_2O$

| | C | H | N | O |
|---|---|---|---|---|
| Calculated | 53.3 | 9.5 | 3.9 | 33.3 |
| Found | 53.3 | 9.6 | 3.9 | 33.2 |

Example 4: Preparation of N-2-ethyl-hexyloxycarbonyl-N-methyl-D-glucamine

The procedure is carried out as in Example 3, starting from 0.125 mole 2-ethyl-hexyloxycarbonyl chloroformate prepared as in Example 1-A. Yield 58%.

Melting point: 77°C

The $H^1$ and $C^{13}$ NMR spectra are in conformity with the structure of the product.

Elemental analysis:

| | C | H | N | O |
|---|---|---|---|---|
| Calculated | 54.7 | 9.5 | 4.0 | 31.8 |
| Found | 54.5 | 9.6 | 4.0 | 31.7 |

Example 5: Preparation of N-butanoyl-D-glucosamine

15 g D-glucosamine hydrochloride are solubilized in 150 ml methanol at ambient temperature. After addition of an equivalent of sodium methylate and filtration of the sodium chloride generated, 14.8 ml butyric anhydride are added gradually to the reaction medium which is then stirred for 3 hours at ambient temperature. A precipitate forms which is collected by precipitation then washed and recrystallized in 130 ml hot ethanol. 8.8 g N-butanoyl-D-glucosamine is thus recovered (yield 51%).

Melting point: 212°C

The $H^1$ and $C^{13}$ NMR spectra are in conformity with the structure of the product.

Elemental analysis:

| | C | H | N | O |
|---|---|---|---|---|
| Calculated | 48.2 | 7.7 | 5.6 | 38.5 |
| Found | 48.4 | 7.8 | 5.7 | 38.3 |

Tests:

Used for the performance of the tests are rabbit erythrocytes marketed by the Biomerieux company

under the reference no. 72291. These erythrocytes are used in 50% suspension in water. The lectin used is Banderia simplicifolia isolectin B4, marketed by the SYGMA company.
All the solutions are diluted in phosphate buffer containing calcium and magnesium.

A. Hemagglutination by lectin:

The lectin is put into solution in phosphate buffer at a concentration of 1 mg/ml. 25 $\mu$l phosphate buffer is distributed into all the wells of the microtitration plates. Into the second well are added 25 $\mu$l of the lectin to be tested. After homogenization, 25 $\mu$l from this well are transferred into the next well and so on so as to obtain successive dilutions. The erythrocytes are diluted to 1/10 (fresh solution). 5 $\mu$l of the suspension and 5 $\mu$l of the content of a well are placed on a slide. After mixing by rotation it is observed whether there is hemoagglutination or not. This develops in 5 min at a maximum. In this way, the minimum quantity of lectin that permits a clear erythrocyte hemagglutination to be obtained is measured.

B. Inhibition of the hemagglutination

After having measured the minimum quantity of lectin permitting a clear erythrocyte hemagglutination to be obtained, double the concentration is chosen for the test. Into the microtitration plates is placed 25 $\mu$l phosphate buffer as a negative control. Into the other wells are distributed 25 $\mu$l of lectin at the predetermined concentration. Into the second well is added 25 $\mu$l phosphate buffer to obtain a positive control. Into the third well is placed 25 $\mu$l the carbohydrate derivative to be tested, in solution at a concentration of 0.1M. After homogenization, 25 $\mu$l is taken from this well and placed in the next and so on so as to obtain successive dilutions. After having left the lectin and the carbohydrate derivative in contact for 30 min at ambient temperature, 5 $\mu$l is placed on a slide and mixed with 5 $\mu$l erythrocyte suspension. It is observed whether or not there is hemagglutination after agitation by rotation.

C. Results

The lowest dilution of carbohydrate that permits an inhibition of hemagglutination to be observed is measured. The result is given as a fraction (corresponding to the dilution) of the initial concentration (0.1 M).

1) Products according to the invention

6'-O-octanoyl-D-maltose: 1/4
N-2-ethylhexyloxycarbonyl-N-methyl-D-glucamine: 1/16
N-octyloxycarbonyl-N-methyl-D-glucamine: 1/64

2) Product according to the prior art:

N-acetyl-D-glucosamine: no inhibition observed for the undiluted solution (concentration: 0.1 M)

It can thus be concluded from these results that the compounds according to the invention are more efficacious than the products described in the prior art (Brysk, Cell and tissue research 253, 657-663, 1988).

Examples of compositions:

These examples illustrate the invention. The proportions indicated are percentages by weight.

Composition 1: O/W emulsion

Phase A:

| | | |
|---|---|---|
| 6'-O-Octanoyl-D-maltose | | 2.5 |
| Sweet almond oil | | 14.5 |
| Shea oil | | 7.0 |
| PPG-3 myristyl ether (EMCOL 249-3K) | | 5.0 |
| Preservative (propylparaben) | | 0.1 |
| Polysorbate 60 (TWEEN 60) | | 2.5 |
| Sorbitan stearate (SPAN 60) | | 2.5 |

Phase B:

| | | |
|---|---|---|
| Cyclomethicone | | 4.0 |
| Xanthan gum | | 0.2 |
| Carboxyvinyl polymer | | 0.5 |

Phase C:

| | | |
|---|---|---|
| Triethanolamine (neutralizer) | | 0.5 |
| Water | | 2.0 |

Phase D:

| | | |
|---|---|---|
| Preservative (methylparaben) | | 0.2 |
| Glycerin | | 5.0 |
| Water | qsp | 100 |

Method:

The constituents of Phase A are fused at 85°C, then Phase A is cooled to 70°C and Phases B then C and D are introduced with stirring. The mixture is cooled to ambient temperature. A day cream is obtained which causes exfoliation of the skin and thus imparts to it a smoother, younger appearance than before treatment.

Composition 2: Gel

| | | |
|---|---|---|
| N-2-ethyl-hexyloxycarbonyl-N-methyl-D-glucamine | | 5.0 |
| Hydroxypropylcellulose (Klucel H from the Hercules company) | | 1.0 |
| Antioxidant | | 0.05 |
| Isopropanol | | 40.0 |
| Preservative | | 0.3 |
| Water | qsp | 100 |

A gel is obtained which on regular application permits skin spots to be faded by exfoliation.

Composition 3: Solution for dermatological application

| | | |
|---|---|---|
| N-Octyloxycarbonyl-N-methyl-D-glucamine | | 5.00 |
| Antioxidant | | 0.05 |
| Ethyl alcohol | | 10.00 |
| Preservative | | 0.30 |
| Water | qsp | 100 |

Application of this solution under dermatological control makes it possible to obtain a profound exfoliation of the corneal layer and thus the initiation of a process of epidermal repair having as its final therapeutic effect an erasing of spots and discolorations, a fading of wrinkles and lines and an improvement in the clinical state of the skin, the appearance of which becomes that of younger skin.

This application is performed in one to three weekly sessions for 4 to 6 weeks.

## Claims

1. Use in or for the production of a topical composition for the promotion of the exfoliation of the skin of at least one carbohydrate or carbohydrate derivative corresponding to the formula (I),

R-X-A (I)

in which A represents a chain composed of one to twenty carbohydrate or carbohydrate derivative units, each containing 3 to 6 carbon atoms, linked to each other, preferably by acetal bridges, each of these units possibly being substituted by a halogen, amine function, acid function, ester function, thiol, alkoxy function, thio-ether function, thio-ester function, amide function, carbamate function, or urea function,

R represents an alkoyl chain or an alkenyl chain containing 4 to 24 carbon atoms, branched or linear, able to be interrupted by ether bridges, possibly bearing a hydroxyl function, a carboxylic acid function, an amine function, an ester function, an acyloxy function, an amide function, an ether function, a carbamate function, or a urea function,

X represents a function linking R and A.

2. Use in accordance with claim 1 to treat skin aging.

3. Use in accordance with one of the claims 1 and 2, characterized by the fact that X is an amine, ether, amide, ester, urea, carbamate, thioester, thioether or sulfonamide function.

4. Use in accordance with any one of the claims 1 to 3, characterized by the fact that the units composing A are linked together by acetal bridges.

5. Use in accordance with any one of the claims 1 to 4, characterized by the fact that each of the carbohydrate units composing A is a sugar or sugar derivative.

6. Use in accordance with any one of the claims 1 to 5, characterized by the fact that at least one of the units composing A is chosen from among the reduced sugars, amino sugars and sugars bearing a carboxylic acid function.

7. Use in accordance with any one of the claims 1 to 4, characterized by the fact that R represents an alkoyl or alkenyl chain containing 4 to 24 carbon atoms, branched or linear, bearing a hydroxyl function.

8. Use in accordance with any one of the claims 1 to 7, characterized by the fact that the units composing A are chosen from among: N-acetyl-D-galactosamine, N-acetyl-D-glucosamine, -acetylneuraminic acid, adonitol, β-D-allose, D-altrose, 6-amino-6-deoxy-D-glucose, 1,6-anhydroglucose, arabinic acid, arabinogalactan, D-arabinose, L-arabinose, D,L-arabinose, D-arabitol, L-arabitol, D-cellobiose, D-glucosamine, D-galactosamine, 2-deoxyD-glucose, 6-deoxy-D-galactose, 6-deoxy-L-galactose, galactitol, mesoerythritol, D-erythrose, D-fructose, D-fucose, L-fucose, D-galactaric acid, galactitol [sic], galactomannan, D-galactono-1,4-lactone, L-galactono-1,4-lactone, D-galactosamine, D-galactose, L-galactose, D-galacturonic acid, β-gentobiose, glucamine, D-glucaric acid, D-glucaric acid [sic], D-glucono-1,5-lactone, L-glucono-1,5-lactone, D-glucosamine, D-glucosaminic acid, D-glucuronic acid, L-glucose, D-glucose, isomaltitol, isomaltotriose, isomaltose, lactobionic acid, D-lactose, lactulose, D-lyxose, L-lyxose, lyxosamine, maltitol, D-maltose, maltotetraose, maltotriitol, maltotriose, D-mannosamine, D-mannose, L-mannose, D-melezitose, D-melibiose, D-raffinose, D-raffinose undeca-acetate, L-rhamnose, D-ribose, L-ribose, D-ribulose, D-threose, turanose, D-xylitol, D-xylose, L-xylose, D,L-xylose.

9. Use in accordance with any one of the claims 1 to 8, characterized by the fact that A is chosen from among:
D-glucosamine, D-glucamine, N–methyl-glucamine, D-glucose, D-maltose, sorbitol, and maltitol.

10. Use in accordance with any one of the claims 1 to 9, characterized by the fact that R contains 4 to 16 carbon atoms.

11. Use in accordance with any one of the claims 1 to 10, characterized by the fact that (I) is chosen from among:
N-butanoyl-D-glucosamine, N-octanoyl-D-glucosamine, N–octyloxycarbonyl-N-methyl-D-glucamine, N-2-ethyl-hexyloxycarbonyl-N-methyl-D-glucamine, 6-O-octanoyl-D-glucose, 6'-O-octanoyl-D-maltose, 6'-O-dodecanoyl-D-maltose.

12. Use in accordance with any one of the claims 1 to 11, characterized by the fact that the carbohydrate in accordance with (I) or the mixture of carbohydrates in accordance with (I) is present in a quantity of from 0.05 to 20% by weight relative to the total weight of the composition.

13. Use in accordance with any one of the claims 1 to 12, characterized by the fact that the carbohydrate in accordance with (I) or the mixture of carbohydrates in accordance with (I) is present in a quantity of from 0.2 to 10% and preferably 0.5 to 5% by weight relative to the total weight of the composition.

14. Use in accordance with any one of the claims 1 to 13, characterized by the fact that the topical composition also includes at least one other active substance having exfoliating properties.

15. Use in accordance with any one of the claims 1 to 14, characterized by the fact that the topical composition also contains α-hydroxyacids or β-hydroxyacids, which can be linear, branched or cyclic, saturated or unsaturated, the hydrogen atoms of the carbon chain being able to be substituted by halogens, halogenated, alkylated, acylated, acyloxylated, alkoxy- carbonylated or alkoxylated radicals having 2 to 18 carbon atoms.

16. Use in accordance with any one of the claims 1 to 15, characterized by the fact that the composition also contains at least one product chosen from among the fruit acids, salicylic acid as well as its alkyl, acyl or alkoxyl derivatives, retinoic acid (all-trans or 13-cis) and its derivatives, retinol (Vitamin A) and its esters as well as their salts, and retinal.

17. Use in accordance with any one of the claims 1 to 16, characterized by the fact that the composition also contains at least one product chosen from among
glycolic, lactic, malic, tartaric, citric acids, mandelic, salicylic acids, n-octanoyl-5-salicylic acid, n-dodecanoyl-5-salicylic acid, n-decanoyl-5-salicylic acid, n-octyl-5-salicylic acid, n-heptyloxy-5- or -4-salicylic acid, 2-hydroxy-3-methylbenzoic acid, 2-hydroxy-3-methoxybenzoic acid, retinoic acid (all-trans or 13-cis), retinol (Vitamin A), retinol palmitate, retinol acetate, retinol propionate as well as their salts, and retinal.

18. Use in accordance with any one of the claims 1 to 17, characterized by the fact that the composition also contains, in addition to the carbohydrate or carbohydrates according to (I), at least one other compound with exfoliating properties, representing from 0.01 to 5% by weight of the total weight of the composition, and more preferably from 0.1 to 3%.

19. Use in accordance with any one of the claims 1 to 18, characterized by the fact that the composition also contains at least one additional sun screen, active in the UVA and/or UVB, hydrophilic or lipophilic, and possibly including a sulfonic function.

20. Use in accordance with any one of the claims 1 to 19, characterized by the fact that the composition also contains at least one antagonist of substance P and/or of CGRP.

21. Use in accordance with any one of the claims 1 to 20, characterized by the fact that the composition also contains at least one product chosen from among Iris Pallida and the strontium salts, in particular the chlorides and nitrates of strontium.

22. Method of cosmetic treatment of the skin intended for the exfoliation of the skin, consisting of applying to the skin a composition containing at least one carbohydrate according to (I).

23. Method of cosmetic treatment of the aging of the skin, consisting of applying to the skin a composition containing at least one carbohydrate according to (I), in a cosmetically and/or dermatologically acceptable medium.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 96/01522

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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|---|---|---|
| X | FR,A,2 703 993 (L'ORÉAL) 21 October 1994<br>cited in the application<br><br>see claims 1-4<br>see page 9, line 16-21<br>see examples J,K,V<br>see page 3, line 11-16<br>see page 6, line 19 - line 23<br>see page 7, line 3-31 | 1-3,<br>6-10,12,<br>13,15,<br>17,19 |
| X | WO,A,95 05155 (L.ROBERT, A.ROBERT) 23<br>February 1995<br><br>see claims 1,2,4,5,8 | 1-3,5-7,<br>10,12,<br>13,22,23 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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